

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BV-1074 WO	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/SE2004/000590	International filing date (<i>day/month/year</i>) 15.04.2004	Priority date (<i>day/month/year</i>) 24.04.2003
International Patent Classification (IPC) or national classification and IPC C07D493/04, 317/48, 493/14, 493/14, 491/153, C07C49/213, A61K31/343, 31/121 31/36, 31/4355, 31/353, A61P5/06, 9/10, 17/06, 35/00		
Applicant Biovitrum AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☐ (*sent to the applicant and to the International Bureau*) a total of _____ sheets, as follows:

☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (*sent to the International Bureau only*) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input checked="" type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

Date of submission of the demand 10.11.2004	Date of completion of this report 18.08.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Per Renström/Els Telephone No. +46 8 782 25 00

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on:

- ☐ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

- ☒ the international application as originally filed/furnished
- ☐ the description:
- pages _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ the claims:
- pages _____ as originally filed/furnished
- pages* _____ as amended (together with any statement) under Article 19
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ the drawings:
- pages _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-7, 15-16; 8-14 partly

because:

☒ the said international application, or the said claims Nos. 1-7, 15-16
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv) : Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-6, 8-16
are so unclear that no meaningful opinion could be formed (*specify*):

Present claims 1-6 and 8-16 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the
.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 1-16 partly (non-unity)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-bis of the Administrative Instructions.

☒ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: BOX No. III

compounds. The present claims are also so wide that a meaningful search over their whole scope is impossible. The search has therefore been carried out for those parts of the claims which appear to be supported and disclosed, namely the following:

the parts of claims 1-6 and 12-16 relating to those compounds of formula IV in claim 6 that have oxygen substituents (e.g. -O-alkyl) in positions R_4 , R_5 and R_{10} ,

the parts of claims 1-6 and 8-16 relating to those compounds of formula III in claim 8 for which R_4 and R_5 (same or different) are hydroxy or methoxy and for which R_9 , R_{10} and R_{11} is methoxy,

the parts of claims 1-6 and 8-16 relating to those compounds of formula I in claim 10 for which R_4 and R_5 (same or different) are hydroxy or methoxy and for which R_9 , R_{10} and R_{11} are methoxy,

the parts of claims 1-6 and 8-16 relating to derivatives of podophyllotoxin which derivatives only differ from podophyllotoxin in that the methylenedioxy group is exchanged for R_4 and R_5 (same or different) = hydroxy, methoxy, ethoxy, propoxy or isopropoxy, in that the methoxy groups on the free benzene ring may be exchanged for any oxygen substituents including -O-alkyl and bridges such as methylenedioxy groups, and in that R_{17} and R_{18} may only be hydrogen or hydroxy.

Furthermore, present claims 1-6 and 12-14 relate to methods and uses defined by reference to a desirable characteristic or property, namely inhibition of tyrosine phosphorylation of the insulin-like growth factor-1 receptor. In their present wording the claims may relate to a large number of different disorders which are not clearly defined by the fact that they might be treated by inhibition of said receptor. The claims do not meet the requirements of Article 6 PCT that claims shall be clear and concise.

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Box No. IV Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:
 - ☐ restricted the claims
 - ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ neither restricted the claims nor paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
 - ☐ complied with
 - ☒ not complied with for the following reasons:

The International Search Authority considers that there are 2 inventions covered by the claims, indicated as follows:

(Invention 1) The parts of claims 1-16 directed to derivatives of the compounds in WO2102804 and WO2102805 in which derivatives the methylenedioxy group corresponding to R₄ and R₅ is opened or exchanged for another functionality, which parts are represented by the example 4,5-demethylene-deoxypodophyllotoxin (Figure 2) and Compounds IA (Figure 3), Compounds IIIA and IIIC (Figure 5) and Compounds IVA, IVC and IVE (Figure 6).

(Invention 2) The parts of claims 1-16 directed to derivatives of the compounds in WO2102804 and WO2102805 which derivatives are substituted on the benzene ring in the position corresponding to R₇ (such as Compounds IB, IC and ID in Figure 3), on the carbon between the rings in the position corresponding to R₁ and/or R₂ (such as Compounds IE and IF in Figure 3) or in both of these positions (such as Compounds IIA-IIF in Figure 4; Compounds IIIB and IIID-IIIF in Figure 5; Compounds IVB, IVD and IV F in Figure 6 and the picropodophyllin- and picropeltatin derivatives in Figure 7).

.../...

4. Consequently, this report has been established in respect of the following parts of the international application:
 - ☐ all parts
 - ☒ the parts relating to claims Nos. Invention 1 as described above

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: BOX No. IV

The ISA has carried out a partial search which relates to invention 1 mentioned above.

The present application has been considered to contain 2 inventions which are not linked such that they form a single general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT, for the following reasons:

Both inventions relate to the problem of providing alternative, selective IGF-1R-inhibitors to the ones known from WO02102804 and WO02102805. Invention 1 solves this problem by exchange or opening of the methylenedioxy group that is characteristic for the podophyllotoxin derivatives. Invention 2 solves the problem by modification of the known podophyllotoxin derivatives in the part of the molecule consisting of the second ring in the naphthalene moiety, attached to the methylenedioxybenzene ring through R_7 and to the methylene bridge between the methylenedioxybenzene ring and the free (trimethoxy-)benzene ring through R_1/R_2 .

Since the solutions are technically different, no single general concept can be formulated based on the technical features of the inventions. Consequently, the requirements of Rule 13.1 PCT are not met. It was investigated under Rule 13.2 if any further features, either in the claims or derivable from the description, could be considered as a same or corresponding feature and which could be considered a special technical feature establishing a technical link between the two groups of inventions. However, no such features were identified.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>9, 12-14, partly</u>	YES
	Claims	<u>8, 10-11</u>	NO
Inventive step (IS)	Claims	<u>-</u>	YES
	Claims	<u>8-14</u>	NO
Industrial applicability (IA)	Claims	<u>8-14</u>	YES
	Claims	<u>-</u>	NO

2. Citations and explanations (Rule 70.7)

Relevant documents

D1) WO 02102804 A1 (KAROLINSKA INNOVATIONS AB),
27 December 2002 (27.12.2002)

D2) WO 02102805 A1 (KAROLINSKA INNOVATIONS AB),
27 December 2002 (27.12.2002)

D3) J. Med. Chem., Vol. 44, 2001, Anne Dantzig et al:
"Cytotoxic Responses to Aromatic Ring and
Configurational Variations in alpha-Conidendrin,
Podophyllotoxin, and Sikkimotoxin Derivatives",
sid 180 - sid 185

D4) J. Med. Chem., Vol. 39, 1996, Tameo Iwasaki et al:
"Novel Selective PDE IV Inhibitors as Antiasthmatic
Agents. Synthesis and Biological Activities of a
Series of 1-Aryl-2,3-bis(hydroxymethyl)naphthalene
Lignans", sid 2696 - sid 2704

D5) STN International, File CAPLUS, CAPLUS accession
no. 2002:298301, Document no. 137:185295,
Basavaraju, Y. B. et al: "Synthesis of analogues of
podophyllotoxin: Tetralones as intermediates for
the synthesis of analogues of
Beta-apopicropodophyllin"; & Indian Journal of
Heterocyclic Chemistry (2002), 11(3), 229-232

D6) STN International, File CAPLUS, CAPLUS accession
no. 1967:411054, Document no. 67:11054, Swan, R. J.
et al: "Optical rotatory dispersion studies. XLI.
The absolute configuration of plicatic acid";
& Canadian Journal of Chemistry (1967), 45(3),
319-24

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: V

D7) STN International, File CAPLUS, CAPLUS accession no. 1963:461993, Document no. 59:61993, Schreier, E.: "Natural products inhibiting mitoses. XI. Structure of sikkimotoxin. 1. Synthesis of stereoisomeric 6,7-dimethoxy analogs of podophyllotoxin"; & Helvetica Chimica Acta (1963), 46, 75-117

D8) STN International, File CAOLD, CAOLD accession no. CA65:2187d, Braun, Loren L. et al: "2-(2-carboxyethyl)amino-1,4-naphthoquinone derivs"

D1 and D2 disclose cyclolignan derivatives that are close analogues to the compounds in the application and like these are inhibitors of tyrosine phosphorylation of the IGF-1 receptor and useful in the treatment of cancer and other IGF-1R related disorders. The compounds in the application differ from the compounds in D1/D2 in that the methylenedioxy group corresponding to R₄ and R₅ is cleaved or exchanged for (an)other functional group(s). This difference can be said to constitute a solution to the general problem of providing alternative IGF-1R inhibitors.

The only support for the IGF-1R inhibiting activity of the large group of compounds claimed in the present application, however, lies in the reported activity of the only prepared experimental compound being provided, i.e. 4,5-demethylene-deoxypodophyllotoxin. This compound is reported as being a less potent IGF-1R inhibitor than the parent compound podophyllotoxin, while not being shown to have a greater selectivity. In view of this lack of support and the large scope of the claims, the invention according to present claims 8-14 is considered to lack an inventive step with regard to D1, or D2.

D3 (see compound 9) and D4 (see compound 7a) disclose compounds with pharmacological activity, which compounds are included in the scope of present claims 10-11. The invention according to claims 10-11 thereby lacks novelty with regard to D3 and D4, taken separately.

D5-D8 disclose compounds that are included in the scope of claim 8 in the application. The invention according to claim 8 thereby lacks novelty with regard to each of these documents.